A New Role for a Metabolic Star: AMP-Activated Protein Kinase Stimulates Fat Absorption

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AMPK is a kinase involved in cell energy homeostasis. In this issue of *Cell Metabolism*, Chopra and colleagues (2011) reveal a new function of AMPK in stimulating fat absorption. AMPK enhances the expression of the bile acid transporter, BSEP, by activating the coactivator SRC-2, thus promoting bile acid secretion.

Energy regulation is an essential process in all organisms. It is necessary to preserve a constant ATP concentration for metabolic processes at the cellular level and to maintain a balance between energy supply and energy expenditure when considering the whole organism. AMP-activated protein kinase (AMPK) is considered one of the major regulators of cellular and whole-body energy homeostasis. AMPK activation requires the phosphorylation of its α subunit at Thr172 by upstream kinases: LKB1 (liver kinase B1), the main upstream kinase active in the liver, and Ca^{2+}/calmodulin-dependent protein kinase kinase. It is activated by various stresses that increase the cellular AMP/ATP ratio, and its main role is to restore energy homeostasis by slowing down ATP-consuming pathways (e.g., fatty acid synthesis and gluconeogenesis) and activating substrate provision such as glucose transport in muscles and ATP-producing pathways (fatty acid oxidation). AMPK is also involved in whole-body homeostasis, since it integrates many hormonal and adipokine signals (leptin, ghrelin, adiponectin) involved in the central stimulation of food intake (Kahn et al., 2005).

In this issue, O'Malley and colleagues discover a novel function of AMPK in the control of fat absorption (Chopra et al., 2011). They found that hepatic invalidation of the transcriptional coactivator SRC-2 (steroid receptor coactivator-2) in mice is concomitant with a reduced capacity to absorb triglycerides from the gut lumen into the enterocytes. This results in an increased fecal content of triglycerides and decreased plasma triglyceride concentration. Since bile acids (BAs) are necessary for dietary lipid absorption, the authors explored a possible deficiency in BA secretion in hepatic SRC-2 knockout (KO) mice. The SRC-2 KO mice display increased hepatic BA concentrations and decreased biliary BA levels, consistent with a defect in hepatic BA secretion into the gut. Interestingly, the fat malabsorption is completely rescued in SRC-2 KO mice receiving exogenous BAs in their diet, suggesting that SRC-2 regulates BA secretion from the liver to the intestine.

Analysis of BA hepatic transporters revealed a defect in BSEP (bile salt export pump) expression in the liver of SRC-2 KO mice. Accordingly, adenoviral overexpression of BSEP was sufficient to completely reverse triglyceride malabsorption. *BSEP* expression is controlled by the farnesoid X receptor (FXR) (Ananthanarayanan et al., 2001), and the authors found that SRC-2 synergized with FXR for *BSEP* promoter activation. Interestingly, the other members of the p160 family of coactivators, SRC-1 and SRC-3, do not interact with the *BSEP* promoter, confirmed by appropriate BA regulation observed in SRC-1 and SRC-3 KO mice. The authors then hypothesized that since SRC-2 promotes energy intake (increase of fat absorption), this coactivator could itself be regulated by changes in energy status. Indeed, AMPK phosphorylates purified SRC-2 in an AMP-dependent manner, and AMPK activation increased the transcriptional activity of SRC-2. Moreover, both SRC-2 and FXR are required to transmit the AMPK effect to the *BSEP* promoter. Consequently, BSEP expression is strongly induced when AMPK is activated. In addition, BSEP expression is decreased and the hepatic BA content is (modestly) increased in the livers of AMPKα1/α2 double KO mice. In summary, O'Malley and colleagues demonstrate that SRC-2 promotes BA secretion and thus lipid absorption by controlling the expression of the canalicular transporter BSEP. Furthermore, they show that AMPK stimulates the expression of BSEP through SRC-2 activation (Chopra et al., 2011).

Two other recent papers support a role for AMPK in BA metabolism. Fu and colleagues demonstrated that inhibition of the LKB1-AMPK pathway strongly impaired canalicular network formation in rat cultured hepatocytes (Fu et al., 2010), while Woods et al. (2010) used liver-specific LKB1 KO mice to show that LKB1 is necessary for biliary tree and canalicular formation and BA homeostasis. Liver-specific deletion of LKB1 causes a mislocalization of BSEP, from the canalicular membrane to a cytoplasmic localization, resulting in toxic accumulation of BAs in the liver (Woods et al., 2010). In this later study, and in contrast with the work of O'Malley et al., *BSEP* expression is not altered, although AMPK activity is strongly downregulated. Interestingly, in AMPKα1/α2 double KO mice, the expression of *BSEP* is also only modestly altered. These studies suggest that AMPK activation could regulate BSEP at both transcriptional and posttranslational levels in conditions of energy depletion.

This work of Chopra et al. (2011) sheds light on a new role of SRC-2 and AMPK

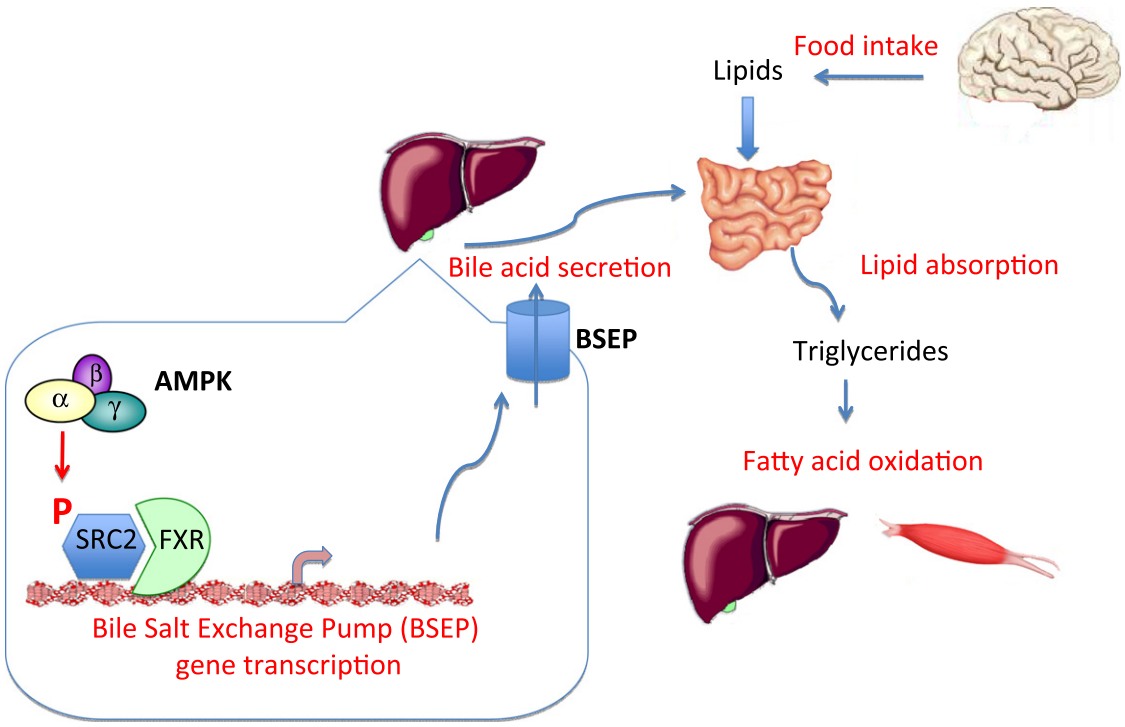

Figure 1. Role of AMPK in Lipid Metabolism

AMP-activated protein kinase (AMPK) is considered a major regulator of cellular and whole-body energy homeostasis. AMPK is involved in the control of whole-body homeostasis by regulating food intake. In the liver and skeletal muscles, AMPK activates ATP-producing pathways such as fatty acid oxidation. In this paper, by studying hepatic SRC-2 KO mice, Chopra et al., (2011) revealed a new function of AMPK in the control of triglyceride absorption. They identified the p160 family member SRC-2 as a new AMPK target protein. SRC-2 phosphorylation by AMPK promotes, in coordination with the FXR nuclear receptor, the transactivation of the BSEP (bile salt export pump) promoter, leading to secretion of BAs into the gut lumen, thus facilitating lipid absorption. AMPK is thus involved in all aspects of lipid metabolism (pathways stimulated by AMPK are labeled with red text).

in the control of lipid availability and raises numerous questions. In addition to decreased *BSEP* expression, SRC-2 KO mice presented a decreased expression of other BA transporters, such as *OSTβ*, *MRP2*, and cholesterol transporters *ABCG5* and *ABCG8* (the last three being members of the ABC transporter family) (Chopra et al., 2011). It would be interesting to study whether AMPK also controls the expression of these transporters, although this might seem paradoxical since most of these transporters are of the ABC family and are consuming ATP to fulfill their role.

Chopra et al. (2011) showed that besides SRC-2, AMPK activation increased the transcriptional activity of the other p160 members, SRC-1 and SRC-3. Since *BSEP* promoter is not a target of SRC-1 and SRC-3, the functional consequences of their activation by AMPK remain to be determined. Since AMPK is shown here to be involved indirectly in energy absorption, studying the role of AMPK in both glucose and lipid absorption in the intestine is also certainly worthwhile. For instance, some studies have shown that AMPK activation increases the localization of the glucose transporter GLUT2 on the apical membrane of enterocytes (Walker et al., 2005; Sakar et al., 2010). This suggests that AMPK could also promote glucose absorption in the intestine. As mentioned previously, whereas the LKB1 KO mice present a severe phenotype of cholestasis, the AMPK double KO mice described (Chopra et al., 2011) have only modest modifications of hepatic and serum BA concentrations. Since LKB1 controls the activity of a family of 13 kinases, including AMPK (Lizcano et al., 2004), this suggests that other kinases of this family could also be involved in BA metabolism.

AMPK was known to activate food intake (and thus lipid provision) and tissue fat oxidation. Chopra et al. (2011), by showing that AMPK also activates intestinal lipid absorption, demonstrate that AMPK is involved in all steps of lipid metabolism, allowing efficient increase of cellular energy provision (Figure 1).

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